(1968).
(44) P. S. Bailey, J. E. Keller, D. A. Mitchard, and H. M. White, *Adv. Chem. Ser.*, **77**, 58 (1968).
(45) F. E. Stary, D. E. Emge, and R. W. Murray, *J. Am. Chem. Soc.*, **98**, 1880 (1976).
(46) F. Kovač and B. Plesničar, *J. Chem. Soc., Chem. Commun.*, 122 (1978).
(47) F. Kovač and B. Plesničar, *J. Am. Chem. Soc.*, **101**, 2677 (1979). They observed singlet O_2 yields by chemical scavenging.
(48) (a) M. E. Kurz and W. A. Pryor, *Tetrahedron Lett.*, 697 (1978); (b) *J. Am. Chem. Soc.*, **100**, 7953 (1978).
(49) Reference 16b, Chapter XV, p 400.
(50) R. F. Hampson, Jr., and D. Garvin, Eds., "Reaction Rate Data and Photochemical Data for Atmospheric Chemistry—1977", *Natl. Bur. Stand.* (*U.S.*), *Spec. Publ.*, **No. 513** (1978).
(51) The O-atom steady-state concentration could not exceed $[O]_{ss} \leq K_{eq} [(O_3)/(O_2)]$, where K_{eq} is for the dissociation reaction (VI) and is equal to $10^{4.8-24/\theta}$ M[49] and $\theta = 2.303RT$ kcal/mol. At 300 K $[O]_{ss} \leq 10^{-10.7}$ M, so that the half-life of a typical RH might be ~5 days for O_3/O_2 ratios of about 4%. At −78 °C, $[O]_{ss} \leq 10^{-21}$ M and any RH reaction is immeasurably slow.
(52) S. W. Benson, *Adv. Chem. Ser.*, **No. 77**, 74 (1968).
(53) S. W. Benson, *J. Chem. Phys.*, **34**, 521 (1961).
(54) S. W. Benson, *Adv. Photochem.*, **2**, 1 (1964).
(55) S. W. Benson and W. B. DeMore, *Annu. Rev. Phys. Chem.*, **16**, 397 (1965).
(56) R. C. Dobson, D. M. Hayes, and R. Hoffman, *J. Am. Chem. Soc.*, **93**, 6188 (1971).
(57) S. W. Benson and A. N. Bose, *J. Chem. Phys.*, **37**, 2935 (1962). See also S. W. Benson and G. R. Haugen, *J. Am. Chem. Soc.*, **87**, 4036 (1965); *J. Phys. Chem.*, **70**, 3336 (1966); **71**, 1735 (1967). It is shown in the above that additional attraction due to mutual polarization is nearly canceled (±2 kcal) by a repulsion term (Born type).
(58) "Tables of Interatomic Distances," *Chem. Soc., Spec. Publ.*, **No. 11** (1958).
(59) J. G. Kirkwood, *J. Chem. Phys.*, **2**, 351 (1934); see also ref 16b, p 534.
(60) S. W. Benson and R. Shaw, "Organic Peroxides", Vol. I, D. Swern, Ed., Wiley, New York, 1970, Chapter 2.
(61) F. Buckley and A. A. Maryott, "Tables of Dielectric Dispersion Data for Pure Liquids and Dilute Solutions," *Natl. Bur. Stand.* (*U.S.*), *Circ.*, **No. 589** (1958).
(62) J. H. Rytting, B. D. Anderson, and T. Higuchi, *J. Phys. Chem.*, **82**, 2240 (1978); G. Brink and L. Glasser, *ibid.*, **82**, 1000 (1978).
(63) S. W. Benson and P. S. Nangia, unpublished work.

Gas-Phase Acid-Induced Nucleophilic Displacement Reactions. Stereochemistry of Inter- and Intramolecular Substitutions at Saturated Carbon[1]

Maurizio Speranza* and Giancarlo Angelini

Contribution from the Laboratorio di Chimica Nucleare del C.N.R.,
Area della Ricerca di Roma, C.P. 10-00016 Monterotondo Stazione, Rome, Italy.

Received March 14, 1979

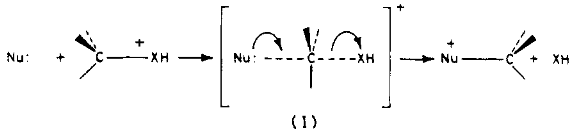
Abstract: The stereochemistry of gas-phase nucleophilic displacement by water on a number of positively charged intermediates was investigated under different experimental conditions. The ionic intermediates were generated in the gas phase at atmospheric pressure by attack of radiolytically formed Brønsted (CH_5^+, $C_2H_5^+$) and Lewis ($C_2H_5^+$, $CH_3FCH_3^+$) acids on selected mono- and bifunctional substrates. Isolation and identification of their neutral substituted products allowed us to demonstrate that, under the used experimental conditions, gas-phase acid-induced inter- and intramolecular nucleophilic displacement reactions occur via predominant (64–98%) *inversion* of configuration at the reaction center. The yield and the stereoisomeric distribution of the substituted products were found to depend on either the nature of the gaseous acid used to generate the charged intermediates or the concentration of the added base (NH_3 or H_2O). Product distribution from bifunctional substrates is characterized by the presence of minor amounts of substituted derivatives retaining the original configuration of their neutral precursors. Their formation is ascribed to the occurrence of an extensive neighboring group participation effect (an HO-3 process) on the displacement reaction, resulting in a double *inversion* of the reaction centers. A mechanistic model is proposed for gas-phase nucleophilic substitutions at atmospheric pressures, and compared with those from related low-pressure ICR (ion cyclotron resonance mass spectrometry) and solution-chemistry studies.

Introduction

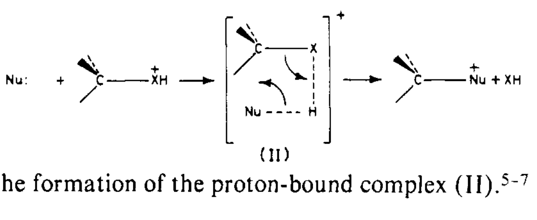
One of the most serious limitations of the mechanistic studies of gas-phase ion–molecule reactions is the almost complete lack of information on the stereochemistry of the processes investigated and the identities of their neutral products. The sporadic application of different experimental techniques, whose common features are the isolation of the neutral products and the determination of their structure, only scratched the surface of this problem. An interesting contribution was provided by a sophisticated trapped-ion ICR experiment carried out by Lieder and Brauman,[2] who elucidated the stereochemistry of a single negative-ion displacement reaction via the detection of the neutral products. However, this powerful technique, as well as other mass-spectrometric approaches, has left many other stereochemical questions unanswered, as demonstrated by the limited number of ion–molecule reaction mechanisms investigated and by the rarity of unambiguous data concerning their stereochemistry. A typical case is represented by the proton-induced nucleophilic displacement reactions at saturated carbon, a process frequently observed in mass spectrometry[3] (Nu: = nucleophile, X = n-donor center, R = alkyl group). As to the mechanism, it is still uncertain whether process (1) involves direct intermolecular substitution (2a),[4]

$$\text{Nu:} + RXH^+ \longrightarrow NuR^+ + XH \qquad (1)$$

i.e., a process corresponding exactly to the S_N2 type of solution chemistry (Walden inversion), or instead the more complex pathway (2b), leading to the retained substituted product via the formation of the proton-bound complex (II).[5-7]



(2a)



(2b)

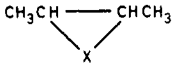
0002-7863/80/1502-3115$01.00/0

Table I. Product Yields from the Gas-Phase Attack of Brønsted and Lewis Acids on Monofunctional Substrates

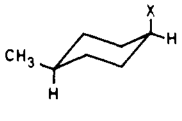
system composition[a]					product yields					total
					meso or cis		*dl* or trans			
substrate (Torr)	CH_4, Torr	CH_3F, Torr	H_2O, Torr	products	$G_{(M)}$[b] $\times 10^2$	rel %	$G_{(M)}$ $\times 10^2$	rel %	inversion/ retention ratio	absolute yield,[c] %
trans-**1** (0.7)	760		2.5	2,3-butanediols	30.0	98	0.7	2	42.9	11.4
cis-**1** (1.4)	760		3.6	2,3-butanediols	0.7	3	26.7	97	38.1	10.1
cis-**2** (0.4)	760		4.0	4-Me-cyclohexanols	0.1	33	0.2	67	2.0	0.1
cis-**2** (0.7)	760		0.9	4-Me-cyclohexanols	3.2	25	9.6	75	3.0	4.6
cis-**2** (0.3)		760	3.0	4-Me-cyclohexanols	0.05	20	0.2	80	4.0	
cis-**2** (0.8)		760	0.6	4-Me-cyclohexanols	0.3	11	2.4	89	8.0	
trans-**3** (0.4)	760		4.0	3-Me-cyclohexanols	0.6	67	0.3	33	2.0	0.3
trans-**3** (0.9)	760		1.2	3-Me-cyclohexanols	2.9	64	1.6	36	1.8	1.6
trans-**3** (0.6)		760	6.0	3-Me-cyclohexanols	0.2	67	0.1	33	2.0	
trans-**3** (0.6)		760	0.8	3-Me-cyclohexanols	0.4	67	0.2	33	2.0	

[a] O_2: 4 Torr. Radiation dose: 4.8 Mrad (dose rate: 0.4 Mrad h^{-1}). [b] $G_{(M)}$ as the number of molecules M produced per 100 eV of absorbed energy. Standard deviation of data ca. 10%. [c] Total absolute yields estimated using $G_{(CH_5^+)} = 1.9 \pm 0.2$ and $G_{(C_2H_5^+)} = 0.9 \pm 0.2$ (ref 12c).

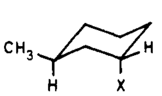
Recently, the stereochemical features of two classes of gas-phase ionic processes, the bimolecular electrophilic substitutions[8] and the cyclization reactions,[9] have been successfully investigated using radiolytic[10] and nuclear-decay[11] methods. In contrast with the classical mass-spectrometric approach, both techniques, in fact, are specifically designed to extend to gas-phase ionic process the methodology typical of solution chemistry, based inter alia on the actual isolation and identification of the neutral products. We, therefore, decided to apply one of these methods to the study of the stereochemistry of process 1 in order to assess the relative importance of the mechanisms 2a and 2b in the nucleophilic substitution reactions. To this end, we selected a set of gaseous acids ($GA^+ = CH_5^+$, $C_2H_5^+$, and $CH_3FCH_3^+$), which can be conveniently produced in known yields by γ-radiolysis of the appropriate neutral precursor (CH_4 or CH_3F).[12] Their attack on the n-donor center (X) of the following neutral substrates RX is expected to generate the corresponding X-protonated,



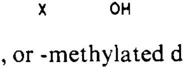
X = O (**1**)



X = Cl (**2**)



X = Cl (**3**)



$CH_3CH(X)CH(OH)CH_3$

X = F (**4**); Cl (**5**); Br (**6**)

-ethylated, or -methylated derivatives (henceforth symbolized as $[RXA]^+$), wherein the potential leaving group XA can be easily displaced by a suitable nucleophile (H_2O):

$$GA^+ + RX \xrightarrow[-G]{} [RXA]^+ \xrightarrow{+H_2O} ROH_2^+ + XA \qquad (3)$$

The Brønsted or Lewis-acid character of GA^+ determines the nature of the moiety A in $[RXA]^+$ and consequently its tendency of establishing with the incoming H_2O the intense electrostatic interaction required to form the complex II.[13]

Finally, the structural features of the selected mono- (**1-3**) and bifunctional (**4-6**) substrates RX may help to elucidate the stereochemistry of inter- and intramolecular nucleophilic substitutions and their relative extent in the bifunctional intermediates. Thus, special attention was devoted in picking out monofunctional substrates (**1-3**), wherein the influence of undesired effects (neighboring-group participation, steric hindrance, conformational shielding, etc.) on the stereochemistry of the displacement process is minimized.

Experimental Section

Materials. Methane, methyl fluoride, oxygen, and ammonia were high-purity gases from Matheson Co., used without further purification. *cis-* and *trans*-2,3-epoxybutanes, *meso-* and *dl*-2,3-butanediols, and the other standards used were research-grade chemicals from Fluka A.G. Isomeric 4- (or 3-) chloro-1-methylcyclohexanes (cis and trans) were prepared from a mixture of *cis-* and *trans*-4- (or 3-) methylcyclohexanols (Hoechst AG) by chlorination with PCl_5[14] and purified by preparative GLC, and their identity was checked by NMR analysis.[15] Addition of hypohalogenous acid on the appropriate isomeric 2-butenes afforded the relative halohydrins in good yields.[16] 3-Fluorobutan-2-ol isomers were prepared by F-to-Cl displacement from anhydrous KF on the appropriate chlorohydrin.[17] Each pair of isomeric halohydrins (erythro and threo forms) was resolved and purified by preparative GLC (5-m 25% Silicone Oil E 301 on Chromosorb W 60-80 mesh, T_c 75 (F), 100 (Cl), 145 °C (Br)), and their identity checked by NMR analysis. All the starting substrates were repeatedly purified and their purity was checked by GLC, using flame ionization detection (FID).

Procedure. The gaseous mixtures were prepared by conventional techniques, using a greaseless vacuum line. The reagents and the additives were introduced into carefully outgassed 1-L Pyrex bulbs, each equipped with a break-seal tip. The bulbs were filled with 1 atm of the appropriate bulk gas (CH_4 or CH_3F), cooled to the liquid-nitrogen temperature, and sealed off. The irradiations were carried out at a temperature of 37.5 °C in a 220 Gammacell from Nuclear Canada Ltd., at a dose rate of 0.4 Mrad h^{-1}, as determined by a Fricke dosimeter. Analyses of the irradiation products were accomplished by injecting known aliquots of the homogeneous gaseous system into a Hewlett-Packard Model 5700 A gas chromatograph, equipped with a FID unit, and their yields determined from the areas of the corresponding eluted peaks, using individual calibration factors.

Results

Table I reports the $G_{(M)}$ values of the products formed from the monofunctional substrates (**1-3**) undergoing gas-phase attack from the radiolytically produced acids, in the presence of water as the nucleophile (eq 3). The data concerning the irradiation of the gaseous mixtures containing the bifunctional substrates (**4-6**) are listed in Table II. The reported results were obtained at a constant dose of 4.8 Mrad (dose rate 0.4 Mrad h^{-1}), and represent the mean values from several separate irradiations carried out under the same conditions. The standard deviation is of the order of 10% except for the lowest values, characterized by a somewhat lower precision. The product yields depend on the composition of the gaseous mixture and,

Table II. Product Yields from the Gas-Phase Attack of $C_nH_5^+$ (n = 1, 2) Ions on Bifunctional Substrates

system composition[a]				G(M) × 10² values of products[b]: 2,3-epoxybutanes		inversion/	2,3-butanediols		inversion/	total absolute
substrate (Torr)	CH_4, Torr	H_2O, Torr	NH_3, Torr	trans (rel %)	cis (rel %)	retention ratio	meso (rel %)	*dl* (rel %)	retention ratio	yields,[c] %
erythro-**4** (2.0)	760	2.2		90.4 (93)	7.2 (7)	12.6	2.4 (73)	0.9 (27)	0.4	36.0
threo-**4** (2.0)	760	2.1		11.2 (12)	86.0 (88)	7.7	0.6 (22)	2.1 (78)	0.3	35.7
erythro-**5** (2.0)	760	1.9		42.4 (89)	5.2 (11)	8.1	0.3 (>97)	n.d.[d] (<3)	<0.1	17.1
erythro-**5** (1.6)	760		0.9	79.4 (92)	7.2 (8)	11.0	n.d.	n.d.		30.8
erythro-**5** (2.3)	760		3.0	76.3 (84)	14.9 (16)	5.1				32.6
erythro-**5** (1.4)	760		10.0	37.9 (87)	5.9 (13)	6.4				15.6
threo-**5** (2.0)	760	1.9		4.0 (9)	39.0 (91)	9.7	n.d. (<2)	0.4 (>98)	<0.1	15.5
threo-**5** (2.0)	760		0.9	5.2 (14)	33.2 (86)	6.4				13.7
threo-**5** (1.5)	760		3.0	4.0 (20)	16.5 (80)	4.1				7.3
threo-**5** (1.6)	760		10.0	2.5 (11)	19.7 (89)	7.9	n.d.	n.d.		7.1
erythro-**6** (1.9)	760	1.8		n.d.	n.d.		n.d.	n.d.		
threo-**6** (2.0)	760	1.9		n.d.	n.d.		n.d.	n.d.		

[a] O_2: 4 Torr. Radiation dose: 4.8 Mrad (dose rate: 0.4 Mrad h^{-1}). [b] $G_{(M)}$ as the number of molecules M produced per 100 eV of absorbed energy. Standard deviation of data ca. 10%. [c] Total absolute yields estimated using $G_{(CH_5^+)} = 1.9 \pm 0.2$ and $G_{(C_2H_5^+)} = 0.9 \pm 0.2$ (ref 12c). [d] n.d. = not detectable ($G_{(M)} = 1 \times 10^{-4}$).

for bifunctional substrates, on the nature of the two basic centers, since each of them faces competition for the acid by both the other basic site of the molecule and the nucleophile(s) deliberately added to the system (H_2O, NH_3) (Tables I and II).

A close inspection of Table II reveals that, under similar experimental conditions, erythro halohydrins give rise to substituted products, whose yield is invariably higher than that of the corresponding threo isomers. In addition, a different effect of ammonia on the substituted products from *erythro*- and *threo*-**5** is observed. Thus, while the 2,3-epoxybutane yield from *threo*-**5** monotonically decreases by increasing NH_3 concentration, the yield of the cyclic products from the erythro isomer reaches the maximum value in the presence of 0.9–3.0 Torr of NH_3.

The major features of the experimental results can be summarized as follows:

(1) The *inverted* product is predominantly formed from the nucleophilic attack of H_2O on protonated and alkylated monofunctional substrates. Moreover, the displacement process is more stereospecific for the methylated compounds than for the protonated ones.

(2) Mainly *inverted* cyclic products are obtained from protonated **4** and **5**. In addition, the nature of the leaving group (HF, HCl) does not affect the stereospecificity of the cyclization process to any appreciable extent.

(3) Protonated bromohydrins do not undergo substitution by the nucleophilic species used in the present study.

(4) Small yields of the 2,3-butanediols with the *original configuration* of the starting halohydrin are formed together with the cyclic products.

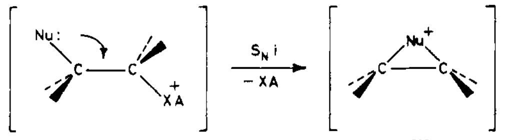
Discussion

Nature of the Displacement Process. As previously outlined in related studies,[8,9,12e,f] the composition of the gaseous reaction mixtures, where the substrate RX is diluted in a large excess of CH_4 (or CH_3F), excludes direct radiolysis of the substrate as a significant route to the observed substituted products. This view is further confirmed by the lack of products from the brominated substrates, which are known to be particularly susceptible to radiolytic decomposition. The presence of an efficient thermal radical scavenger, such as oxygen, in the gaseous samples strongly inhibits possible free-radical channels in favor of the competitive ionic pathways to the substituted products, as testified by the marked effect of ion trappers, such as NH_3 and H_2O, on their overall yield. Therefore, it is suggested that the formation of the substituted products involves preliminary attack of the radiolytic acid(s) GA^+ on the present substrate(s), followed by condensation with a water molecule (eq 3). Several pieces of evidence support this sequence, including the absence of any products from nonirradiated control systems and the formation, in the irradiated samples, of compounds containing an additional oxygen atom, whose yield becomes vanishingly small in the absence of water, even though O_2 is contained in the system. The evident influence of the nature of GA^+ on the product distribution and the significant decrease of the substituted product yields (Table I) by addition of moderate concentrations of water further confirm the proposed mechanism. Such effects should in fact be negligible, if the alternative sequence (4) occurs

$$GA^+ + H_2O \xrightarrow[-G]{} [H_2OA]^+ \xrightarrow{+RX} ROH_2^+ + XA \qquad (4)$$

preferentially in the irradiated systems. In conclusion, the above considerations indicate that the nucleophilic displacements taking place in the present radiolytic systems follow the same mechanistic sequence (eq 3) described in previous mass-spectrometric studies on related inter-[6] and intramolecular[18] processes.

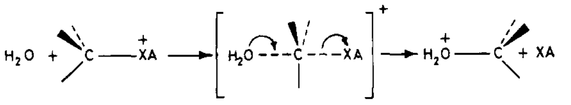
As mentioned before, the major ionic species arising from radiolysis of CH_4[12a,d] are methonium (CH_5^+, $\Delta H_f° = 221$ kcal mol^{-1})[19] and ethyl ($C_2H_5^+$, $\Delta H_f° = 219$ kcal mol^{-1})[19] ions. The role of these cations as gaseous Brønsted acids has been exhaustively demonstrated by chemical ionization mass spectrometry[20] and by independent radiolytic studies.[8] In addition to its Brønsted-acid properties, the ethyl cation may react as a typical Lewis acid, leading to condensation products.[21] Both gaseous acids, thermalized by many unreactive collisions with CH_4, eventually attack the substrates, present in low concentrations in the gaseous mixture. In contrast to the observed random attack of CH_5^+ and $C_2H_5^+$ on alkanes,[22] functionalized molecules, such as those used in the present study, orient the electrophile by electrostatic interactions, so as to undergo a strictly localized attack on their n centers.[20] Dimethylfluoronium ($CH_3FCH_3^+$; $\Delta H_f° = 161 \pm 8$ kcal mol^{-1}) ions, generated in high yields by γ-radiolysis of CH_3F, are known to behave in the same way,[12e,f] their attack on the selected substrate being even less exoergic than that of $C_nH_5^+$.[23] Therefore, the exothermic attack of the gaseous acids on the selected substrates primarily leads to the n-protonated or alkylated intermediates which may follow a variety of reaction pathways, including isomerization,[24] intermolecular attack from any gaseous nucleophile, and unimolecular dissociation.[25] The last process is effectively prevented, in the radiolytic systems, by the efficient collisional deactivation of the excited intermediates. However, the presence, in the bifunctional intermediates (III), of a nucleophilic group adjacent to the reaction center may promote, when energetically allowed, a fast intramolecular displacement, leading to the cyclic species (IV). This process (S_Ni), regarded as a particular



(III) (IV) (5)

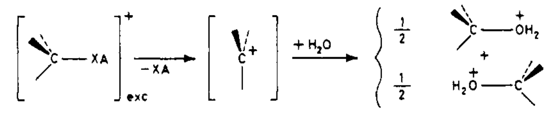
unimolecular dissociation of the bifunctional intermediates (III), has been frequently postulated in related ICR studies.[18b,26]

Nucleophilic Attack on Monofunctional $[RXA]^+$ Intermediates. The results outlined in the previous sections (Table I) give strong support for a displacement mechanism involving a *backside* attack of H_2O on the carbon atom bearing the leaving group, with the predominant formation of the inverted product (eq 2a). The high stereospecificity observed for this



(2a)

class of reactions is consistent with the bimolecular character of the mechanism proposed (eq 2a), ruling out any alternative pathway involving unimolecular dissociation of the intermediates $[RXA]_{exc}{}^+$, excited by the exothermicity of their formation process, before condensation with the nucleophile (eq 2c).[27] The extent of the competitive substitution path (2c) is

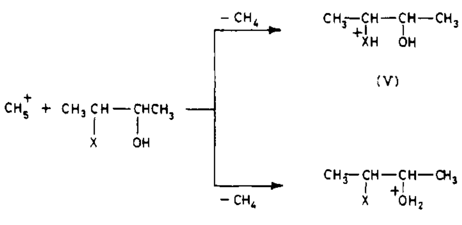


(2c)

limited by the efficient quenching of $[RXA]_{exc}{}^+$ by unreactive collisions with the batch gas molecules, which prevents extensive formation of the planar carbonium ion R^+, the precursor of the racemized substitution product. In this connection, the yield of *retained* product is expected to parallel the excitation energy of $[RXA]_{exc}{}^+$. Indeed, the *inverted vs. retained* product yields ratios from methylated **2** and **3** are higher than those measured from the more excited protonated intermediates.[23] The extremely high stereospecificity of the nucleophilic attack on protonated **1** demonstrates that the displacement process is not assisted by a preliminary coordination of the nucleophile to the OH moiety of the charged intermediate (hydrogen bonding), which would rather favor *frontside* displacement (eq 2b). Further support for this conclusion is provided by the isolation of predominantly *inverted* products from both protonated and methylated **2** and **3**, which indicates that the displacement mechanism is basically independent of the coordinating properties of the A moiety in the corresponding $[RXA]^+$ intermediates.

Thus, gas-phase nucleophilic substitutions on monofunctional $[RXA]^+$ intermediates, i.e., in the absence of neighboring-group effects, take place with *inversion of configuration* of the reaction center. This general conclusion is in full agreement with the stereochemical requirements associated with analogous processes occurring in solution (Walden inversion) and with their theoretical rationalization.[28]

Nucleophilic Attack on Bifunctional $[RXA]^+$ Intermediates. Attack of the gaseous acids on a bifunctional substrate can generate two different ionic intermediates; for instance,[9] see eq 6. Process 6b leads to the formation of oxonium ions (VI), particularly stable under the present experimental conditions.[29] Therefore, although pathway 6b does not produce any observable product, it nevertheless consumes part of the gaseous acid reagent. In fact, the diverse absolute yields measured under almost identical experimental conditions for the three halohydrins (Table II) are indicative of the different branching

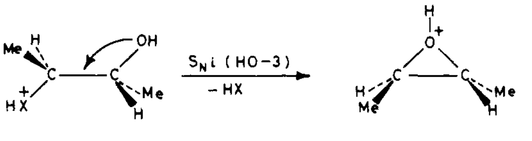


(V) (6a)

(VI) (6b)

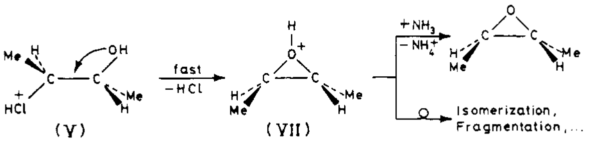
ratios due to the competition of the two basic centers of the bifunctional substrate for the acid reagent ((6a) vs. (6b)).

Isolation of cyclic butene oxides in good yields from the gaseous systems of Table II shows that the halonium ion intermediate (V) undergoes fast intramolecular displacement from the vicinal nucleophilic group (an HO-3 process), e.g., V → VII, involving the intermediacy of the oxygen-protonated



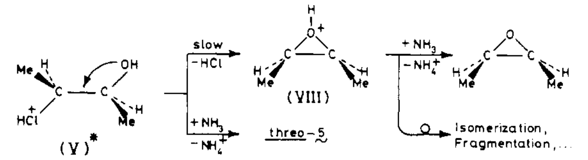
(V) (VII) (5)

butene oxide (VII). The aptitude of V to undergo S_Ni reaction depends on its structure as demonstrated by the higher yields of epoxybutane from the erythro halohydrins when compared to those from the corresponding threo forms. This different tendency is reflected in the particular effect of the NH_3 concentration on the epoxybutane yields from erythro and threo chlorohydrins (Table II). Protonated *erythro*-**5** readily produces VII (eq 7a), which gives the neutral derivative by proton



(V) (VII) (7a)

transfer to NH_3. Thus, addition of limited concentrations of base favors neutralization with respect to the competitive isomerization or fragmentation pathways. However, at high NH_3 concentrations, this effect is counterbalanced by the effective NH_3 trapping of the GA^+ acids, resulting in an overall decrease of the epoxybutane yields. On the other hand, the small aptitude of protonated *threo*-**5** to undergo cyclization exposes it to fast deprotonation by addition of even limited concentrations of NH_3 (eq 7b). As a consequence, a monotonic

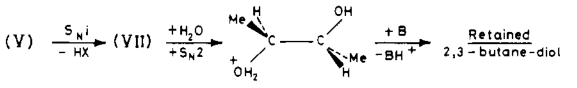


(V)* (VIII) (7b)

decrease of epoxybutane yield is observed by increasing the NH_3 concentration. The presence of two eclipsed methyl groups in VIII from *threo*-**5** may be responsible for the small tendency of protonated *threo*-**5** (V*) to undergo the S_Ni process. Incidentally, the total absolute yields listed in Table II indicate, in agreement with other radiolytic[30] and mass-spectrometric[18b,31] data, that in the halogen series HF is the best leaving group, while HBr is not displaced at all by the present nucleophiles.[26]

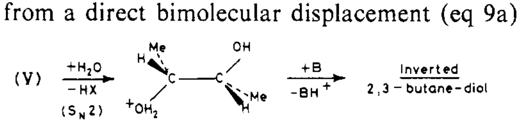
According to the general behavior observed in the intermolecular substitutions (see previous section), intramolecular displacement processes (5) also result in *inversion of the configuration* of the reaction centers, as can be seen from the isomeric distribution of the butene oxides formed.

This conclusion, coupled with the remarkable stereoselectivity observed in the acid-induced ring opening of 2,3-butene oxides (Table I), suggests that the formation of the *retained* glycols of Table II is mainly attributable to a sequence of two nucleophilic displacements resulting in a *double inversion of configuration* of the reaction center(s), e.g., eq 8. On the other hand, the small yields of *inverted* butene glycol can arise either from a direct bimolecular displacement (eq 9a) and/or, as previously pointed out, from the unimolecular dissociation of the protonated halohydrin with formation of a free carbonium ion (X). Under the present experimental conditions, this is expected to give rise to a *meso*- and *dl*-2,3-butanediol mixture.



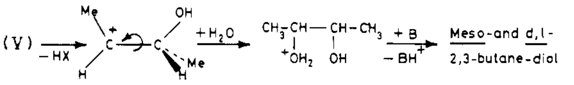
(8)

B = base (IX)



(9a)

(inverted IX)

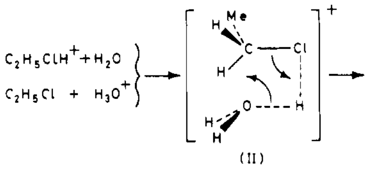


(9b)

(X) ("racemized"-IX)

As a whole, the present results demonstrate that gas-phase acid-induced inter- and intramolecular nucleophilic substitutions proceed mainly via inversion of configuration of the reaction center, and that, when structurally possible, intramolecular processes predominate over intermolecular ones.

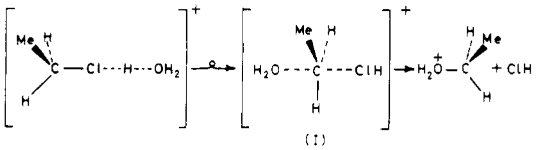
Comparison with Related Reactions Studied by ICR Mass Spectrometry. From his ICR studies on acid-induced nucleophilic displacement reactions (eq 1),[6] Beauchamp concluded that the electrostatic interactions (hydrogen bonding) between the neutral nucleophilic and the protonated substrate lead to the formation of an intimate reaction complex (II), e.g., eq 2b.



(2b)

(II)

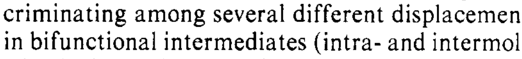
According to its geometry, the encounter complex (II) is expected to lead to the substituted product ($C_2H_5OH_2^+$) via a *frontside* displacement, which in a chiral molecule should cause the *retention* of the configuration of the reaction site. However, Beauchamp's ICR data could also be accommodated by a stepwise process, involving a fast proton transfer from the less to the more basic center of the encounter complex and the *subsequent* backside attack of the neutral formed on the protonated substrate, for instance, eq 10. The energy requirements associated with both reaction sequences ((2b) and (10)) are essentially the same, since in both cases the free energy gain from the hydrogen-bond interaction in the encounter complex must be almost completely lost as the nucleophile approaches the reaction site, on account of the necessary large hydrogen-bond distortion from linearity. On the other hand, Beauchamp's data seem to exclude any conceivable direct substitution (S_N2 type) without the preliminary establishment of a hydrogen-bond interaction (process 2b).



(10)

(I)

Thus, from the ICR evidence and the present high-pressure data, we propose a mechanistic model for gas-phase acid-induced nucleophilic substitutions occurring at atmospheric pressures. Long-range electrostatic interactions between [RXH^+] and the nucleophile lead predominantly to the formation of the proton-bound cluster [$RX\cdots H\cdots Nu$]$^+$.[13,32] In the high-pressure radiolytic systems, characterized by the efficient collisional deactivation of the reactive intermediates, the formed cluster can neither readily[33] dissociate to give the proton-transfer products ($RX + HNu^+$) nor undergo large hydrogen-bond angle distortion, as in II, but rather its stability is such as to allow attack by *another* molecule of nucleophile.[33] The present stereochemical study demonstrates that the H_2O molecule approaching the cluster from its unshielded side (the R group) is likely to displace the leaving group via the inversion of the configuration of the C center (eq 11). In other words, those proton-bound clusters, which escape dissociation because collisionally deactivated, undergo nucleophilic displacement with inversion of configuration.



(11)

The proposed gas-phase substitution model finds interesting analogies in solution chemistry. In fact, in the protolytic halogen displacement in primary and secondary alkyl fluorides, essentially the same transition state of eq 11 has been proposed on account of the general acid catalysis and autocatalysis observed for these reactions.[34]

In conclusion, ICR and radiolytic evidence provides strong support for a nucleophilic displacement mechanism dominated by electrostatic interactions at very low pressures (ICR), whereas at higher pressures (radiolysis) the formation of proton-bound clusters and their collisional deactivation promote nucleophilic displacement involving the direct attack of an external molecule of nucleophile on the ionic intermediate, leading to *inversion of configuration* of the reaction center, much like analogous solvolytic processes in the condensed phase. These findings are of particular interest since they refer to reactions occurring in a medium free from the effects of the solvent and of the counterion which considerably complicate similar processes occurring in solution. The possibility of discriminating among several different displacement pathways in bifunctional intermediates (intra- and intermolecular substitution), on the grounds of isomer distribution, allows the evaluation of neighboring group participation phenomena in the gas phase. Thus, the role of the solvent in anchimerically assisted reactions can be directly determined by comparing the gas-phase data with those from the corresponding solvolytic systems.

Acknowledgment. The authors are grateful to F. Cacace for stimulating discussions on the subject of this paper.

References and Notes

(1) Presented in part at the 4th International Symposium on Physical Organic Chemistry, York, U.K., Sept 1978.
(2) Lieder, C. A.; Brauman, J. I. *J. Am. Chem. Soc.* **1974,** *96,* 4028.
(3) For a review, see: Richter, W. J.; Schwarz, N. *Angew. Chem., Int. Ed. Engl.* **1972,** *17,* 424.
(4) Haegele, K. D.; Desiderio, D. M., Jr. *J. Org. Chem.* **1974,** *39,* 1078.
(5) The enthalpy difference between the separated reactants of (1) and the encounter complex ranges around 25–30 kcal/mol (ref 6e).
(6) (a) Holtz, D.; Beauchamp, J. L.; Woodgate, S. D. *J. Am. Chem. Soc.* **1970,** *92,* 7484. (b) Holtz, D.; Beauchamp, J. L. *Nature* (*London*), *Phys. Sci.* **1971,** *231,* 204. (c) Beauchamp, J. L.; Holtz, D.; Woodgate, S. D.; Patt, S. L. *J. Am. Chem. Soc.* **1972,** *94,* 2798. (d) Staley, R. H.; Cordeman, R. R.; Foster, M. S.; Beauchamp, J. L. *Ibid.* **1974,** *96,* 1260. (e) Beauchamp, J. L. "Interactions between Ions and Molecules", Ausloos, P., Ed.; Plenum Press: New York, 1975.
(7) Weinkam, R. J.; Gal, J. *Org. Mass Spectrom.* **1976,** *11,* 197.
(8) Cacace, F.; Speranza, M. *J. Am. Chem. Soc.* **1972,** *94,* 4447.
(9) Angelini, G.; Speranza, M. *J. Chem. Soc., Chem. Commun.* **1978,** 213.
(10) For reviews, see: (a) Ausloos, P. *Annu. Rev. Phys. Chem* **1966,** *17,* 205. (b) *Prog. React. Kinet.* **1969,** *5,* 113. (c) Ausloos, P.; Lias, S. G. "Ion-Molecule Reactions", Franklin, J. L., Ed.; Plenum Press: New York, 1972. (d) Cacace, F. "Kinetics of Ion-Molecule Reactions", Ausloos, P., Ed.; Plenum Press: New York, 1979.

(11) For reviews, see: (a) Cacace, F. "Proceedings of the Conference on the Methods of Preparing and Storing Marked Molecules"; Euratom: Bruxelles, 1964. (b) *Adv. Phys. Org. Chem.* **1970,** *8,* 79. (c) In ref 6e. (d) "Hot Atom Chemistry Status Report"; IAEA: Vienna, 1975.

(12) (a) Ausloos, P.; Lias, S. G.; Scala, A. A. *Adv. Chem. Ser.* **1966,** *No. 58,* 264. (b) Ausloos, P. In ref 10c. (c) Ausloos, P.; Lias, S. G.; Gorden, R., Jr. *J. Chem. Phys.* **1963,** *39,* 3341. (d) *Ibid.* **1964,** *40,* 1854. (e) Colosimo, M.; Bucci, R. *J. Phys. Chem.* **1979,** *83,* 1952. (f) Speranza, M.; Pepe, N.; Cipollini, R. *J. Chem. Soc., Perkin Trans. 2* **1979,** 1179.

(13) (a) Yamdagni, R.; Kebarle, P. *J. Am. Chem. Soc.* **1973,** *95,* 3504. (b) Grimsrud, E. P.; Kebarle, P. *Ibid.* **1973,** *95,* 7939. (c) Hiraoka, K.; Grimsrud, E. P.; Kebarle, P. *Ibid.* **1974,** *96,* 3359. (d) Hiraoka, K.; Kebarle, P. *Ibid.* **1977,** *99,* 360.

(14) (a) Goering, H. L.; Mc Carron, F. H. *J. Am. Chem. Soc.* **1956,** *78,* 2270. (b) Goldberg, S. I.; Sahli, M. S. *J. Org. Chem.* **1967,** *32,* 2059.

(15) (a) Lemieux, R. U.; Kullnig, R. K.; Bernstein, H. J.; Schneider, W. G. *J. Am. Chem. Soc.* **1958,** *80,* 6098. (b) Brownstein, S.; Miller, R. *J. Org. Chem.* **1959,** *24,* 1886. (c) Dupuy, W. E.; Hudson, H. R.; Karam, P. A. *J. Chromatogr.* **1972,** *71,* 347.

(16) Coleman, G. H.; Johnstone, H. F. "Organic Syntheses", Collect. Vol. I; Wiley: New York, 1941; p 151.

(17) Hoffman, F. W. *J. Am. Chem. Soc.* **1948,** *70,* 2596.

(18) (a) Wieting, R. D.; Staley, R. H.; Beauchamp, J. L. *J. Am. Chem. Soc.* **1974,** *96,* 7552. (b) Kim, J. K.; Findlay, M. C.; Henderson, W. G.; Caserio, M. C. *Ibid.* **1973,** *95,* 2184.

(19) (a) Chupka, W. A.; Berkowitz, J. A. *J. Chem. Phys.* **1971,** *54,* 4256. (b) Jelus, B. L.; Murray, R. K., Jr.; Munson, B. *J. Am. Chem. Soc.* **1975,** *97,* 2362.

(20) For reviews, see: (a) Field, F. H.; Munson, M. S. B.; Becker, D. A. *Adv. Chem. Ser.* **1966,** *58,* 167. (b) Field, F. H. in "Ion-Molecule Reactions", Franklin, J. L., Ed.; Butterworths: London, 1972; Vol. I, p 261.

(21) Cacace, F.; Cipollini, R.; Giacomello, P.; Possagno, E. *Gazz. Chim. Ital.* **1974,** *104,* 977. The condensation intermediate $[RXC_2H_5]^+$ may undergo nucleophilic displacement by H_2O as well.

(22) (a) Munson, M. S. B.; Field, F. H. *J. Am. Chem. Soc.* **1966,** *88,* 2621. (b) Houriet, R.; Gaumann, T. *Int. J. Mass Spectrom. Ion Phys.* **1978,** *28,* 93.

(23) Protonation by CH_5^+ and $C_2H_5^+$ on the n centers of the selected substrates is computed to release 40–50 and 0–10 kcal mol^{-1}, respectively. Condensation of $C_2H_5^+$ is exothermic for ca. 20 kcal mol^{-1}. The energy release from methylation by $CH_3FCH_3^+$ of the used compounds is only 10–20 kcal mol^{-1}.

(24) Isomerization of $[RXA^+]$ is an extensive process depending upon the exothermicity of its formation reaction. The extent of isomerization of $[RXA^+]$ and the consequent isomeric distribution have been thoroughly investigated and will be presented in a separate paper.

(25) In agreement with thermochemical calculations on molecules structurally related to those of the present study, the unimolecular dissociation of $[RXA^+]_{exc}$, excited by the exothermicity of its formation process, is energetically allowed, except when the gaseous acid is $CH_3FCH_3^+$. The extent of unimolecular dissociation in analogous ionic intermediates has been extensively investigated by mass spectrometry and found to be related to the proton affinity of the leaving group. (a) Reference 18b. (b) Jardine, I.; Fenselau, C. *J. Am. Chem. Soc.* **1976,** *98,* 5086.

$$[RXA^+]_{exc} \rightarrow R^+ + XA$$

(26) Berman, D. W.; Anicich, V.; Beauchamp, J. L. *J. Am. Chem. Soc.* **1979,** *101,* 1239.

(27) A stereospecificity below 20% is expected from rough calculations, made assuming complete dissociation of $[RXA]^+_{exc}$, before condensation with the present nucleophiles (H_2O and RX itself).

(28) Klopman G., Ed. "Chemical Reactivity and Reaction Paths"; Wiley: New York, 1974.

(29) The nucleophilic attack of water on the oxonium ions from processes 6b is energetically unfavorable in the gas phase, as demonstrated by the lack of inverted starting material, when even a thermoneutral H_2O-to-H_2O displacement is allowed.

(30) (a) Cacace, F.; Speranza, M. *J. Am. Chem. Soc.* **1976,** *98,* 7299. (b) Speranza, M.; Cacace, F. *Ibid.* **1977,** *99,* 3051.

(31) Speranza, M.; Sefcik, M. D.: Henis, J. M. S.; Gaspar, P. P. *J. Am. Chem. Soc.* **1977,** *99,* 5583.

(32) Maot-Ner, M.; Field, F. H. *J. Am. Chem. Soc.* **1977,** *99,* 998.

(33) As a matter of fact, endothermic proton transfer from $[RXH^+]$ to Nu as well as $[RX \cdots H \cdots Nu]^+$ dissociation can be promoted if clustering of a sufficient number of molecules of nucleophile occurs (ref 13d and Attinà, M.; Cacace, F.; Ciranni, G.; Giacomello, P. *J. Chem. Soc., Chem. Commun.* **1978,** 938).

(34) For a review, see: Ingold, C. K. "Structure and Mechanism in Organic Chemistry"; Cornell University Press: Ithaca, N.Y., 1969; p 478.

Gas-Phase Acylation Reactions. Substrate and Positional Selectivity of Free Acetylium Ions toward Methylbenzenes

Maurizio Speranza* and Cinzia Sparapani

Contribution from the Laboratorio di Chimica Nucleare del C.N.R.,
00016 Monterotondo Stazione, Rome, Italy.

Received July 9, 1979

Abstract: Free acetylium ions, obtained in the diluted gas state from the γ radiolysis of CH_3F–CO mixtures, have been allowed to react with methylbenzenes, in the pressure range 380–760 Torr, and in the presence of a gaseous base (NH_3). The gaseous cation has been confirmed to be unreactive toward benzene and toluene, whereas it acetylates the xylenes and the other selected polymethylated benzenes. The relative rates of acetylation have been determined in competition experiments, using mesitylene as the reference substrate. The mechanism of acetylation and subsequent isomerization is discussed, and the substrate and positional selectivity of the free CH_3CO^+ ion are evaluated, together with its intrinsic steric requirements. Comparison of the gas-phase results with those of related condensed-phase reactions, involving CH_3CO^+ salts as one of the reactive species, reveals no basic mechanistic differences. Some observed reactivity and selectivity discrepancies, in particular those concerning acetylation of toluene, *o*- and *m*-xylene, and hemimellitene, are outlined and their possible causes considered.

Introduction

In a previous paper, the application of specifically designed radiolytic and nuclear methods to generate free acetylium (CH_3CO^+) ions in the diluted gas state has been reported.[1] It has been shown that, independently of their origin, gaseous acetylium ions display features typical of a mild electrophile, as evidenced by their unreactivity toward unactivated π-type substrates, such as benzene and toluene. Only n-donor nucleophiles (aliphatic alcohols) and activated arenes (anisole and phenol) undergo attack by thermal CH_3CO^+ ions, yielding the corresponding acetylated derivatives. Gas-phase condensation reactions between ground-state[2] CH_3CO^+ and the above-mentioned substrates could not be observed in independent ICR experiments.[3,4]

The growing interest attached to directive effects in the gas-phase aromatic substitutions, i.e., in the absence of solvation, ion pairing, etc.,[5] has stimulated further work aimed to assess the *intrinsic* reactivity and selectivity of a well-defined gaseous cation, the CH_3CO^+ ion, toward increasingly substituted and activated arenes, in order to determine the reactivity limits of the electrophile and its positional selectivity.

The resulting information is expected to contribute to the rationalization of condensed-phase acetylation reactions, usually complicated by the diverse mechanisms occurring simultaneously in such systems and by the largely variable reactivity and steric requirements attributed to the postulated acetylation reactants.[6]

In the present paper, we describe the results of related

0002-7863/80/1502-3120$01.00/0